CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

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RISK ASSESSMENT and RISK MITIGATION REVIEW(S)

Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology
Office of Medication Error Prevention and Risk Management

Risk Evaluation and Mitigation Strategy (REMS) Review

Date:	January 22, 2016
Reviewer(s):	Erin Hachey, Pharm.D. Division of Risk Management (DRISK)
Acting Team Leader:	Jamie Wilkins Parker, Pharm.D., DRISK
Acting Deputy Director:	Kellie Taylor, Pharm.D., M.P.H., DRISK
Division Director:	Cynthia LaCivita, Pharm.D., DRISK
Subject:	Evaluation to determine if a REMS is necessary
Drug Name(s):	Taltz (ixekizumab)
Therapeutic Class:	Interleukin (IL)-17A antagonist
Dosage and Route:	Two 80 mg subcutaneous injections at week 0, followed by one 80 mg injection at Weeks 2, 4, 6, 8, 10, and 12, then 80 mg every 4 weeks
Application Type/Number:	BLA 125521
Applicant:	Eli Lilly and Company
OSE RCM #:	2015-799

Table of Contents

1 INTRODUCTION

This review by the Division of Risk Management (DRISK) evaluates if a risk evaluation and mitigation strategy (REMS) is necessary for the new molecular entity (NME), Taltz (ixekizumab) solution for injection. A biologic license application (BLA 125521) for ixekizumab was received on March 23, 2015 from Eli Lilly and Company (Eli Lilly). The proposed indication for ixekizumab is the treatment of adult patients with moderate-to-severe plaque psoriasis who are candidates for systemic therapy or phototherapy. The Applicant did not submit a proposed REMS, but did submit a proposed risk management plan as part of the submission.

1.1 DISEASE BACKGROUND

Psoriasis is a common, chronic, inflammatory, multi-system disease with predominantly skin and joint manifestations. It can present in many different patterns from the scalp to the feet and cause psychiatric distress and physical disabilities. Psoriasis affects approximately 2–3% of the U.S. population. It can begin at any age, but one population study of the age of onset revealed two peaks, at age 16 and at age 60. Risk factors may include family history, obesity, smoking and environmental smoke, and heavy alcohol use. Risk factors that may trigger or exacerbate psoriasis include stress, physical trauma to the skin, cold dry weather, sun exposure and hot weather, infections, and certain medications. Moderate-to-severe psoriasis is a serious and, at times, disabling condition that has a substantial impact on patients' lives. There are multiple drugs approved for psoriasis that have an acceptable risk-benefit profile and achieve moderate-to-high efficacy for the treatment of moderate-to-severe disease. All of the approved products have significant risks, and there is room for both more efficacious and potentially safer products for these patients.[1,2]

Currently approved drugs for the treatment of moderate-to-severe psoriasis include the anti-metabolite methotrexate (MTX), tumor necrosis factor (TNF) inhibitors, such as etanercept, adalimumab and infliximab, IL-12+23 antagonist ustekinumab, IL-17A antagonist secukinumab, T-cell inhibitor cyclosporine (CSA), retinoid acitretin and phosphodiesterase-4 (PDE-4) inhibitor apremilast (See Table 1). Phototherapy, either PUVA (UVA light combined with the psoralen methoxsalen) or UVB light therapy, is also a standard of care treatment for moderate-to-severe psoriasis patients. The efficacy of these products is generally measured on the Psoriasis Area and Severity Index (PASI), with the change from baseline as the most common primary efficacy endpoint. The PASI 75 (75% reduction in the PASI score compared to baseline) for currently available drug therapies varies from highly efficacious (PASI 75 $\geq$ 70%) for cyclosporine, infliximab, adalimumab, ustekinumab and secukinumab to moderately efficacious (PASI 75 $\geq$ 40%)

[1] Usatine, Richard P., et al. "Chapter 152. Psoriasis." The Color Atlas of Family Medicine, 2e. Eds. Richard P. Usatine, et al. New York, NY: McGraw-Hill, 2013. n. pag. AccessMedicine. Web. 6 Oct. 2015. http://accessmedicine.mhmedical.com/content.aspx?bookid=685&Sectionid=45361214.

[2] Liedtka J. DDDP. Clinical Review for Ixekizumab, BLA 125521, dated November 20, 2015.

for methotrexate and etanercept, to somewhat efficacious (PASI 75 ≥ 20%) for acitretin and apremilast.[3]

Table 1: Drugs FDA Approved for the Treatment of Plaque Psoriasis

Drug	Topical	Oral	Injectable
Acitretin		✓	
Adalimumab			✓
Apremilast		✓	
Calcipotriene	✓		
Calcipotriene/betamethasone dipropionate	✓		
Calcitriol	✓		
Cyclosporine		✓	
Desoximetasone		✓	
Dexamethasone sodium phosphate			✓
Etanercept			✓
Infliximab			✓
Methlyprednisolone		✓	✓
Tazarotene	✓		
Triamcinolone hexacetonide			✓
Ustekinumab			✓

Infliximab, etanercept, and adalimumab were all approved with a REMS which consisted of a Medication Guide (MG) and communication plan (CP) to address the risks of infections and malignancies. The CP REMS for all three drugs were released from their REMS requirements in 2011 because the CP activities were completed and the REMS assessments demonstrated that the REMS goals were being met. The MG remains a part of the labeling for each of these drugs.

The ustekinumab REMS was originally approved in 2009 with a MG, CP, and timetable for assessments. The REMS was required to address the risks of serious infections, malignancy, and reversible posterior leukoencephalopathy syndrome. The Agency approved a modification on May 2, 2012, to remove the MG from the REMS. The 3-year REMS assessment concluded that the ustekinumab REMS was meeting its goals of evaluating and mitigating potential risks of serious infections, malignancy, and reversible posterior leukoencephalopathy syndrome by alerting and warning healthcare providers.[4] The Agency approved a second modification on September 20, 2013, to update REMS materials to include information for a new indication of psoriatic arthritis (PsA), and added rheumatologists as a new target prescriber population. Therefore, an evaluation of rheumatologists' understanding of the risks was added as a part of the assessment plan. The timetable for submission of assessments was not changed. The CP activities for ustekinumab were completed in September 2014, and rheumatologists' knowledge of the risks will be assessed in the next REMS assessment report.

[3] Liedtka J. DDDP. Clinical Review for Ixekizumab, BLA 125521, dated November 20, 2015.

[4] Cvetkovich, T. DRISK Review of 3-year REMS Assessment Report, dated November 30, 2012.

1.1 PRODUCT BACKGROUND

Ixekizumab is a humanized immunoglobulin G subclass 4 (IgG4) monoclonal antibody (mAb) that binds with high affinity and specificity to the cytokine interleukin (IL)-17A. Ixekizumab is an NME and is not currently marketed inside or outside of the U.S. The proposed indication is the treatment of adult patients with moderate-to-severe plaque psoriasis who are candidates for systemic therapy or phototherapy. The proposed dosing regimen is 160 mg by subcutaneous injection (two 80 mg injections) at week 0, followed by an 80 mg injection at Weeks 2, 4, 6, 8, 10, and 12, and then 80 mg every 4 weeks. The proposed methods of dose delivery include a single-dose 80 mg/mL prefilled autoinjector (AI) and a single-dose 80 mg/mL prefilled syringe (PFS), each to deliver 80 mg ixekizumab.

1.2 REGULATORY HISTORY

October 29, 2014: A Pre-BLA meeting was held between the Agency and the Applicant. The Agency advised the Applicant that a REMS was not expected to be necessary, but the final determination for the need for a REMS would be made during the review of the application.

March 23, 2015: The Applicant submitted original BLA 125521 to the Agency. The Applicant did not submit a proposed REMS, but did include a risk management plan in their submission.

June 24, 2015: The Agency sent an information request to the Applicant, requesting the Applicant to conduct a retrospective evaluation of suicidal ideation and behavior associated with ixekizumab using the Columbia Classification Algorithm of Suicide Assessment (C-CASA) for all subjects exposed to ixekizumab.

August 8, 2015: The Applicant responded to the June 24, 2015 information request with their C-CASA analysis.

August 14, 2015: The Mid-Cycle Communication was held between the Agency and the Applicant via teleconference. The Agency communicated to the Applicant that, at this time, there were no plans to require a REMS for ixekizumab, pending the final outcome of the suicidal ideation and behavior analysis.

September 4, 2015: The Applicant submitted additional clinical information in response to the Agency's Mid-Cycle Communication, to further assist with review of the C-CASA analysis.

October 19, 2015: The Agency sent an information request to the Applicant, requesting the C-CASA reports for the placebo and etanercept active comparator groups.

October 26, 2015: The Applicant responded to the October 19, 2015 information request with the C-CASA reports for the placebo and etanercept active comparator groups.

December 2, 2015: The Late-Cycle meeting was held between the Agency and the Applicant.

2 MATERIALS REVIEWED

The following is a list of materials used to inform this review:

- Eli Lilly and Company. Ixekizumab, BLA 125521 submission, received March 23, 2015 (Seq. 0001).
    - Section 1.16, Risk Management Plan
    - Section 2.5, Clinical Overview
    - Section 2.7.4, Summary of Clinical Safety
- Eli Lilly and Company. Four-Month Safety Update Report, received July 22, 2015 (Seq. 0007).
- Eli Lilly and Company. Ixekizumab, BLA 125521 response to information request, received August 6, 2015 (Seq. 0012).
- Eli Lilly and Company. Ixekizumab, BLA 125521 response to information request, received September 4, 2015 (Seq. 0016).
- Eli Lilly and Company. Ixekizumab, BLA 125521 response to information request, received October 26, 2015 (Seq. 0023).
- Alfaro C. Division of Psychiatry Products Consultative Review and Evaluation of Clinical Data, dated August 7, 2015.
- Anic G. Division of Epidemiology Review of Clinical Trial Data, dated October 15, 2015.
- Liedtka J. Division of Dermatology and Dental Products, Clinical Review, BLA 125521, dated November 20, 2015.

3 RESULTS OF REVIEW

3.1 OVERVIEW OF CLINICAL PROGRAM

The Applicant sought to establish psoriasis efficacy results with three phase 3 clinical studies (RHAZ, RHBA, and RHBC). The co-primary efficacy endpoints for these pivotal studies were the proportion of subjects achieving a static Physician Global Assessment (sPGA) score of 0 (clear) or 1 (minimal) with at least a 2-point improvement from baseline at Week 12, and the proportion of subjects achieving a $\geq$ 75% improvement in Psoriasis Area and Severity Index (PASI) 75 from baseline at Week 12.

The first trial, RHAZ, was a multicenter, randomized, double-blind, placebo-controlled, parallel group, outpatient study to determine the efficacy and safety of ixekizumab compared to placebo in subjects with moderate-to-severe plaque psoriasis (Ps). Trial RHAZ included an induction dosing period (IDP), with the primary endpoint evaluated at 12 weeks, followed by a randomized maintenance dosing period (MDP) to Week 60, and a subsequent long-term extension (LTE) period. The MDP evaluated the efficacy and safety of ixekizumab, as well as relapse or rebound following treatment withdrawal, and response to re-treatment following relapse. In addition, longer-term efficacy and safety were evaluated for up to a total of five years in the LTE period for patients who participated through the entire study.

The induction dosing period began with a total of 1296 subjects, randomized on 80 mg ixekizumab every 2 weeks (Q2W) (n=433), 80 mg ixekizumab every 4 weeks (Q4W) (n=432), or placebo (n=431), each as a subcutaneous (SC) injection. Subjects who tolerated treatment and achieved satisfactory efficacy with ixekizumab during the IDP were re-randomized to one of three arms (80 mg Q4W, 80 mg every 12 weeks (Q12W), or placebo) during the MDP. Non-responders from the IDP were assigned to the 80 mg Q4W arm. The trial results demonstrated that all dosing regimens of ixekizumab were statistically superior to placebo ($p < 0.001$).

The second pivotal trial, RHBA, was a multicenter, randomized, double-blind, placebo-controlled study comparing the efficacy and safety of ixekizumab to the active comparator, etanercept, and placebo in patients with moderate to severe Ps. Trial RHBA included a 12-week induction dosing period, followed by a maintenance dosing period to continue to Week 60. The details of the study design are similar to Trial RHAZ, with the exception of the addition of the active comparator, etanercept, arm. The IDP began with 1224 subjects randomized to one of four treatment groups: 80 mg ixekizumab Q2W (n=351), 80 mg ixekizumab Q4W (n=347), etanercept (n=358), or placebo (n=168). A blinded MDP followed the IDP, using 80 mg ixekizumab Q4W, 80 mg ixekizumab Q12W, or placebo.

The primary objectives of the trial were to assess whether 80 mg ixekizumab Q2W or Q4W was:

- Superior to placebo at Week 12
- Non-inferior to etanercept at Week 12
- Superior to etanercept at Week 12

The MDP of this study was still ongoing at the database lock for the Applicant's study report on October 1, 2014. At that time, the last patient completed Week 36. Results demonstrated that both dosing regimens of ixekizumab were statistically superior ($p < 0.001$) to placebo. The proportion of subjects taking etanercept at Week 12 with an sPGA of 0 or 1 was 36% and a PASI 75 was 42%. Both dosage regimens of ixekizumab were statistically superior ($p < 0.001$) to both etanercept and placebo for both of the co-primary efficacy endpoints.

The third pivotal trial, RHBC, was a 12-week, multicenter, randomized, double-blind, placebo-controlled study, similar in design to trial RHBA, with the exception of a lack of a maintenance period. Trial RHBC consisted of an IDP, with the primary endpoint evaluated at 12 weeks. 1346 subjects were randomized into four arms of the study: 80 mg ixekizumab Q2W (n=385), 80 mg ixekizumab Q4W (n=386), etanercept (n=382), and placebo (n=193). Study results demonstrated that both dosage regimens of ixekizumab were statistically superior ($p < 0.001$) to etanercept and placebo.

3.2 OVERVIEW OF SAFETY

The total safety population (n=4736) for ixekizumab was populated from 7 psoriasis trials and 4 rheumatoid arthritis (RA) trials. It included 4204 psoriasis patients and 532 RA patients. Of the 4204 psoriasis subjects exposed to at least one 80 mg dose of ixekizumab, 2190 were exposed for at least one year on the proposed dosing regimen. The most common adverse events (AEs) reported, which occurred in ≥1% of

ixekizumab-treated subjects, and more frequently than in placebo-treated subjects, were injection site reactions, upper respiratory tract infections, nausea, oropharyngeal pain, and tinea infections.

3.2.1 Serious Adverse Events (SAEs)

The exposure-adjusted incidence rate for overall SAEs (patients having at least one SAE) among ixekizumab-treated patients in the MDP was 8.1%, and the rate in the IDP was 8.6%. In the All-Psoriasis Ixekizumab Exposures Integrated Analysis Set (n=4204), the largest analysis set, the exposure-adjusted incidence rate for overall SAEs was 6.4%, with the greatest incidence rate (1.5%) occurring in the infections and infestations system-organ class (SOC).

In the induction dosing period of the three pivotal studies, the SAEs that occurred in more than one subject in the ixekizumab arms were cellulitis, appendicitis, Crohn's disease, and depression. The incidence of serious AEs was similar in the ixekizumab (2.0%) and placebo (1.5%) arms. The incidence of discontinuations due to AEs was numerically slightly higher for the combined ixekizumab treatment arms (ixekizumab 2.1% vs placebo 1.1%), but the difference was not statistically significant.

In the maintenance dosing period of the pivotal studies, there was no significant difference in the incidence of SAEs reported between the ixekizumab group and placebo group (8.1% of both groups reported SAEs). Across all studies, AEs leading to study drug discontinuation were uncommon, and the percentages were generally similar between treatment groups within each study.

There were a total of 13 deaths reported in the ixekizumab clinical development program. Ten deaths were reported in the initial submission of the BLA. One of these was in a subject with psoriasis who had not been randomized to treatment. Of the remaining nine deaths in the initial submission, five were in psoriasis subjects on ixekizumab, three in rheumatoid arthritis (RA) subjects on ixekizumab, and one in a subject on etanercept in trial RHBC. There were no deaths in placebo subjects or during the induction dosing period for subjects on treatment. An additional three deaths in subjects exposed to ixekizumab were reported in the 4-month safety update. None of the three additional cases were definitively related to ixekizumab, according to both the Applicant and the clinical reviewer.

Severe Adverse Events

There were 3 cases of high grade (≥ Grade 3) neutropenia, all of which were transient. One case reported as Grade 4 in ixekizumab Q4W had a normal neutrophil count one week prior to this report and 48 hours after the report with no associated infection. No SAEs or discontinuations due to cytopenias were reported.

3.2.2 Adverse Events of Special Interest (AESIs)

3.2.2.1 Suicidal Ideation and Behavior

The ixekizumab pivotal trial protocols attempted to exclude subjects with a history of suicide attempt, uncontrolled neuropsychiatric disease, or frequent active suicidal ideation using the Quick Inventory of Depressive Symptomatology self-rated (16-

question version) (QIDS-SR16). This was administered at screening, baseline, Week 12 (end of the induction dosing period), and every six months thereafter in the long-term extension period. Of note, the QIDS-SR16, is not designed to be used to screen for a history of neuropsychiatric disease or suicidality, as the reference time period for the evaluation includes only the previous seven days, and, therefore, it is possible that several weeks of information may have been missed. Subjects were excluded from participation in the trials if they had a score of 3 or greater on Item #12 ("Thoughts of death or suicide") at screening or baseline. Regardless, the Applicant reported nine suicide attempts in subjects treated with ixekizumab in the pivotal trials; however, there were no completed suicides.

Due to this finding, and concerns of suicidality with another product currently under review that blocks IL-17A, DDDP requested consultative reviews of the ixekizumab clinical trial data from both the Division of Psychiatry Products (DPP) and the Division of Epidemiology (DEPI).

The DPP review concluded that it was not apparent that the Applicant had provided a comprehensive identification of potential suicide/self-injury cases. Therefore, the review could not definitively determine whether or not there was a signal for suicidality associated with ixekizumab use.[5] As a result of this conclusion, the Agency sent an information request to the Applicant on June 24, 2015, requesting the Applicant to conduct a retrospective evaluation of suicidal ideation and behavior using the Columbia Classification Algorithm of Suicide Assessment (C-CASA) for all subjects exposed to ixekizumab. The C-CASA comprehensively assesses suicidal behavior and ideation, permits comparison of findings across research and clinical populations, as well as trends over time, and eliminates the need for further coding of the relevant events.[6,7] The C-CASA is the instrument recommended by the Agency in the draft guidance for industry *Suicidal Ideation and Behavior: Prospective Assessment of Occurrence in Clinical Trials.*

In response to the Agency's request, the Applicant submitted the data retrospectively, evaluated using the C-CASA. The Applicant's analysis showed the overall incidence of suicidal thoughts and behaviors in patients treated with ixekizumab is 9 attempts/6480 patient-years, or a rate of 0.14%. Additionally, this evaluation concluded that suicide attempts in the ixekizumab group were reported only in patients with multiple risk factors. Two of these patients had undisclosed history of past suicide attempts. Other risk factors in these patients included: depression and bipolar disorder, anxiety, alcohol or other substance use disorder, and the presence of major, acute psycho-social triggers.

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[5] Alfaro C. Division of Psychiatry Products Consultative Review and Evaluation of Clinical Data, dated August 7, 2015.

[6] Draft guidance for industry *Suicidal Ideation and Behavior: Prospective Assessment of Occurrence in Clinical Trials.*

[7] Posner, K., et al. (2011). "The Columbia–Suicide Severity Rating Scale: Initial Validity and Internal Consistency Findings from Three Multisite Studies with Adolescents and Adults." American Journal of Psychiatry 168(12): 1266-1277.

DEPI also evaluated the results of the C-CASA analysis provided by the Applicant, as well as summarized available information on suicide rates in psoriasis patients treated with biologics in other clinical trials. This review concluded that data suggest a possible suicide safety signal for ixekizumab.[8]

After initial analysis by DDDP and DEPI, in order to enable a more comprehensive review of the potential risk of SIB for ixekizumab, the DDDP sent an information request to the Applicant, asking they submit exposure-adjusted data for the placebo and etanercept active comparator groups. The Applicant promptly submitted the requested information. Analysis of these data showed the rate of suicidal ideation in the exposure-adjusted placebo group was approximately three-times greater than that of the ixekizumab group.

Therefore, the DDDP clinical reviewer concluded that, following a thoughtful review, "at this time, the data for ixekizumab do not support a causal link between ixekizumab therapy and suicidal events." The reviewer noted that the majority of the suicide attempts occurred outside the induction and maintenance periods. Additionally, the DDDP reviewer concluded that it is not, however, possible to exclude that suicidal ideation may have been underestimated, since the QIDS-SR16 evaluation was performed only at infrequent intervals, and no other direct inquiry for suicidal ideation (active assessment) was performed during the ixekizumab trials. Furthermore, the clinical reviewer added, "The exclusion of subjects with a history of uncontrolled neuropsychiatric conditions, suicide attempts, or a current score of ≥ 3 on item #12 of the QIDS may limit the generalizability of the results with regard to safety in this subpopulation in the post-marketing setting." [9]

3.3 RISK MANAGEMENT PLAN PROPOSED BY THE APPLICANT

The Applicant has proposed a risk management plan that includes a global safety system, and postmarketing AEs will be monitored via routine pharmacovigilance. The Applicant will also conduct an observational postmarketing safety registry to assess serious infections, serious hypersensitivity reactions, inflammatory bowel disease (IBD), and the incidence of adverse events that are infrequent and/or have a long latency period, such as malignancies. The Applicant will continue to monitor all adverse events reported during the long-term extension phases of the pivotal Phase 3 psoriasis studies and all Eli Lilly-sponsored ixekizumab clinical studies. A medication guide (MG) was included in the proposed labeling. The Applicant also proposed Warnings and Precautions in the labeling to communicate the increased risk of infections, hypersensitivity reactions, IBD, and immunizations.

4 DISCUSSION

Moderate-to-severe psoriasis is a serious and, at times, disabling condition that has a substantial impact on patients' lives. The benefits of treatment with ixekizumab were

[8] Anic G. Division of Epidemiology Review of Clinical Trial Data, dated October 15, 2015.

[9] Liedtka J. DDDP. Clinical Review for Ixekizumab, BLA 125521, dated November 20, 2015.

demonstrated by meeting the co-primary endpoints of the clinical trials. Based on these results, ixekizumab was found to be highly efficacious with an acceptable safety profile for the treatment of adult patients with moderate-to-severe plaque psoriasis who are candidates for systemic therapy or phototherapy.

Internal discussions that involved DDDP, DPP, DEPI, the Division of Pharmacovigilance (DPV), and DRISK were held in order to have a greater understanding of the potential risk of suicidal ideation and behavior associated with ixekizumab use. These discussions ultimately concluded that, although there is an imbalance of cases of suicide attempt, the cases are largely confounded by patients with psychiatric comorbidities. The exposure-adjusted data, which shows the incidence of suicidal ideation was three-times greater in the placebo group than the ixekizumab group, and the fact that there were no completed suicides associated with ixekizumab use will likely have an impact on the decision whether or not to include suicidal ideation and behavior in the labeling. The final labeling is still under negotiation at the time of this review.

All other safety concerns associated with the use of ixekizumab for moderate-to-severe psoriasis are well-documented. The safety profile demonstrated for ixekizumab is consistent with the known safety profiles of other systemic agents used for the treatment of moderate-to-severe psoriasis, and includes risks of immunosuppression with the associated risk of serious and, in some cases, opportunistic or unusual infections, reactivation of latent tuberculosis, cytopenias, inflammatory bowel disease and hypersensitivity events. Healthcare providers are familiar with treatment regimens that include immunomodulating agents involving blockade of cytokines in the psoriasis pathogenesis pathway, including IL-17A inhibitors. Furthermore, labeling will include infections, tuberculosis, hypersensitivity, and inflammatory bowel disease in its Warnings and Precautions section. Additionally, the medications infliximab, adalimumab, and etanercept, which had REMS programs to mitigate the risks of infections and malignancies, had their REMS released after the REMS CP requirements were complete; their REMS assessments showed that healthcare professionals understood the key messages regarding ILs and risk of infection. Since the likely prescribers for ixekizumab are the same, DRISK believes that prescribers are aware and knowledgeable about the risks of immunomodulating agents involving blockade of cytokines in the psoriasis pathogenesis pathway, including IL-17A inhibitors. The Applicant included a MG as part of the proposed labeling, to communicate important safety information to patients and their caregivers. Therefore, based on the data currently available, DRISK and DDDP agree that a REMS is not necessary to ensure the benefits outweigh the risks of ixekizumab.

5 CONCLUSION

Ixekizumab has proven to reduce the severity of symptoms in patients with moderate-to-severe plaque psoriasis. Based on the known safety profile for the drug class and the risks associated with ixekizumab from the clinical trials, the benefit-risk profile is acceptable and will be communicated through labeling. In conclusion, based on the currently available data, a REMS is not necessary for ixekizumab, to ensure the benefits outweigh the risks, for the treatment of moderate-to-severe plaque psoriasis.

Please consult DRISK if new safety information becomes available that would necessitate the Agency to re-evaluate the need for a REMS.

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/s/

ERIN M HACHEY
01/22/2016

CYNTHIA L LACIVITA
01/22/2016
Concur